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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/030,832	02/26/98	HANNA M	1488.0950001

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EXAMINER	
LANDSMAN, R	
ART UNIT	**PAPER NUMBER**
1647	20

DATE MAILED: 06/04/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/030,832	HANNA ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *95-147* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *95-147* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Formal Matters

A. Amendment E, filed 3/20/01, has been entered into the record.

B. Claims 95-147 are pending in the application.

Withdrawn Rejections

1. Claim Rejections - 35 USC § 112, first paragraph – lack of written description

A . The rejection of claims 95, 98, 101, 104, 107-117 and 119-126 under 35 USC 112, first paragraph, has been withdrawn since, even though the specification has not taught the artisan how to make a functional protein which is at least 95% identical to SEQ ID NO:42, the artisan would know the structure of the polynucleotides which encode an amino acid sequence which is at least 95% identical to SEQ ID NO:42. The Examiner appreciates that Applicants addressed the polynucleotides as being the subject of this rejection and not the polypeptides.

2. Claim Rejections - 35 USC § 112, second paragraph

A. All rejections under 35 USC 112, second paragraph, have been withdrawn since Applicants have removed reference to the "Bestfit" program in the claims.

Maintained Objections

A. The specification remains objected to for the reasons already of record on page 6 of the Office Action dated 12/20/00 and for the reasons stated below in the rejection under 35 USC 101.

Maintained Rejections

1. Claim Rejections - 35 USC § 101

A. Claims 95-147 remain rejected under 35 USC 101 for the reasons already of record on pages 4-5 of the Office Action dated 12/20/00. These claims are directed to isolated polynucleotides encoding supposed GABA-A receptor ε-subunit, fragments thereof, vectors, host cells and methods of making vectors and proteins. The specification discloses the isolation of several polynucleotide clones encoding proteins of SEQ ID NO:41 and 42 which have significant sequence similarity to known GABA receptor subunits (page 94, line 20-28 of the specification). Based on the structural similarity, the specification asserts that the polypeptides encoding SEQ ID NO:41 and 42 are GABA receptor subunits.

Applicants argue that if the invention is useful for any particular practical purpose then a rejection based on a lack of utility should not be imposed. Applicants state that GABRE and ET2 *likely* enhance the binding affinity of the receptor complex to various ligands [emphasis added], but no experimental data has been provided demonstrating that the receptors of the present invention have this activity. The assertion that the disclosed proteins have biological activities similar to known GABA receptor subunits cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. Example 6 on page 94-96 of the specification discloses that the transfection of the ε-subunit into cells does produce GABA-activated currents (Figure 5) and binding sites (Figure 6). However, it is not clear that polynucleotide of SEQ ID NO:41 is, in fact, this ε-subunit, or is involved in any of these effects.

In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF- family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF- family members BMP-2 and TGF- 1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also

Massague, who reviews other members of the TGF- family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a

small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan the utility of the claimed polynucleotides encoding SEQ ID NO:41 and 42 which are only known to be homologous to GABA receptor subunints. **Furthermore, since the polynucleotides of the invention have no utility, the claimed vectors, host cells, methods of making the vectors and proteins encoded for by the polynucleotides of the invention also have no utility.**

2. Claim Rejections - 35 USC § 112, first paragraph – lack of enablement

A. Claims 95-147 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on page 6 of the Office Action dated 12/20/00. Applicants have argued that a rejection under 35 USC 112 grounded on a lack of utility is not proper unless a 35 USC 101 rejection is proper. However, the rejection is proper for the reasons discussed the rejection under 35 USC 101 has been maintained as discussed above.

B. Claims 95, 98, 101, 104, 107-117 and 119-147 remain rejected for the reasons already of record on pages 6-7 of the Office Action dated 12/20/00. Applicants have argued that the Examiner has drafted the rejection based on polypeptides and that the Applicants are not required to demonstrate enablement for unclaimed material. Applicants, therefore, argue that polynucleotides are enabled and that the "plain and ordinary meaning" of the phrase "at least 95% identical" is clear. Applicants also provide definitions and means to calculate "95% identity." These arguments have been considered, but are not deemed persuasive. Applicants are claiming polynucleotides which encode polypeptides which are "at least 95%

identical" to the polypeptide of SEQ ID NO:42, or fragments thereof (e.g. amino acid residues 1-260). However, Applicants have provided no guidance or working examples of how polynucleotides which encode polypeptides which are "at least 95% identical" to the polypeptide of SEQ ID NO:42, or fragments thereof other than that of SEQ ID NO:41, nor have they taught the artisan how to make a polynucleotide which encodes said polypeptide, or fragment. One in the art would not be able to predict what nucleotide residues could be organized into a polynucleotide which would encode a functional polypeptide encoding a GABA subunit that would be "at least 95% identical" to the polypeptide of SEQ ID NO:42, or fragments thereof. As discussed in the above rejection under 35 USC 101, even single amino acid residue changes can drastically alter the function of a polypeptide. Therefore, it would not be predictable to the artisan as to which nucleotide residues in the polynucleotide encoding SEQ ID NO:42 one can alter to retain its characteristics.

Furthermore, regarding "fragments" Applicants argue that the Examiner is of the position that the specification fails to recite each and every possible sequence encompassed by the claims. However, the Examiner has not argued that the specification fails to recite each and every possible sequence encompassed by the claims, but simply that there is no working examples of polynucleotides encoding *any* fragments which are at least 95% identical to amino acid residues 1-260 of SEQ ID NO:42, nor is there any guidance of how to make polynucleotides which encode functional fragments which are at least 95% identical to residues 1-260 of SEQ ID NO:42. Applicants state that the specification refers to polynucleotide variants as those caused by degeneracy of the genetic code. However, this degeneracy would produce polynucleotides which are 100% identical to SEQ ID NO:42, or to residues 1-260 of SEQ ID NO:42 and would provide no guidance of how to alter the polynucleotide to produce variants which encode polypeptides which are at least 95% identical to SEQ ID NO:42, or to residues 1-260 of SEQ ID NO:42.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
May 31, 2001

Gary L. Kunz

GARY L. KUNZ
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